

# Risk factors for the adverse cardiac outcomes in the patients with Takayasu's arteritis.

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## Research article

**Keywords:** Takayasu's arteritis, Heart, Echocardiography

**Posted Date:** March 11th, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-16850/v1>

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# Abstract

**Background :** This study was aimed to investigate the long-term cardiac outcomes and find out risk factors for the deterioration of cardiac structure and function in patients with Takayasu's arteritis (TAK).

**Methods :** One hundred and ninety-eight TAK patients were recruited in the Department of Rheumatology, Zhongshan Hospital, Fudan University from January 2012 to December 2017. The endpoint of observation was December 31, 2019. Patients were divided into normal, mild-moderate and severe subgroups based on the severity of structural and functional impairment of heart. Comparison of baseline characteristics and treatment among these three subgroups was conducted to identify the risk factors for adverse cardiac outcomes.

**Results :** A total of 60.1% (119/198) of TAK patients exhibited heart involvement on echocardiography at baseline. 70.6% (84/119) and 79.8% (95/119) cases showed pathological valvular and atrioventricular abnormalities, respectively. 68.7% (136/198) of patients were followed up and the median follow-up duration was 28.6 (12.3-43.4) months. 42.7% (58/136) and 22.8% (31/136) of patients had progress in heart's structure and function. Cox regression showed that serum TNF- $\alpha$  level (HR=1.028, p= 0.021), aortic regurgitation (HR=3.109, p<0.001) and ventricular hypertrophy (HR=2.090, p= 0.006) at baseline were risk factors for the deterioration of cardiac structure. The cases with serum TNF- $\alpha$  levels ( $\geq$ 8.1pg/ml), mild aortic regurgitation and ventricular hypertrophy at baseline had highest risk of structural progression at 83.4%. Using normal subgroup as a control, the deterioration of cardiac structure and function was the most severe in the severe subgroup, with hazard ratios of 16.2 (95% CI, 6.0-44.1, p < 0.001) and 9.0 (95% CI, 3.3-24.5, p<0.001), respectively. The deteriorating events typically occurred within 2 years after diagnosis.

**Conclusions :** To find out if there is heart involvement and progress, it's indispensable to regularly monitor the serum TNF- $\alpha$  level and cardiac structure in TAK patients during the long-term follow-up.

## Introduction

Takayasu's arteritis (TAK) is a typically systematic large vessel vasculitis that is characterized by progressive inflammation and fibrosis in the wall of the aorta and its major branches [1, 2]. TAK has apparently ethnic associations, and young Asian women are the predominant patient population [3]. Epidemiologic researches show that TAK has a low frequency of death, but a high risk of organ dysfunction; hence, TAK patients often experience low quality of life over a considerably long period [4]. Heart is one of the important organs commonly attacked in TAK, but the subsequent changes of cardiac involvement remain unclear.

The involvement of heart has been reported in 8.6%-39.9% of TAK patients [5, 6]. TAK-related heart diseases mainly include valvular insufficiency or stenosis, hypertensive heart disease, ischemic cardiomyopathy and so on [7–11]. Different degrees of heart failure occurred frequently in these TAK subgroup patients, which results in poor prognosis even death [12]. However, the majority of recent

studies on the TAK-related heart diseases are case reports, case series, or cross-sectional studies, and it lacks large sample, prospective and dynamic observational studies to determine the development of cardiac involvement and its risk factors. Echocardiography is a widely used noninvasive tool to evaluate heart structural disease and cardiac dysfunction in TAK patients [13, 14].

We therefore designed this prospective study to investigate the characteristics of TAK patients with cardiac involvement and clarify the underlying risk factors for the adverse cardiac outcomes occurring during long-term follow-up.

## Methods

### Patients

Adult (age>18 years) TAK patients who satisfied the 1990 American College of Rheumatology classification criteria were enrolled from the Department of Rheumatology, Zhongshan Hospital, Fudan University, between January 2012 and December 2017 (Figure 1). All the enrolled patients underwent echocardiography and New York Heart Association (NYHA) functional grade evaluation during the first visit.

Kerr score proposed by the National Institutes of Health (NIH) was used to assess the disease activity. Patients who complained of serious infection, tumor, and current or past history of viral myocarditis or other rheumatic diseases were excluded. This study has been approved by the Ethics Committee of Zhongshan Hospital, Fudan University [B2013-115(3)], and written informed consent was obtained from all the participants.

### Clinical database

The clinical records including demographic data (gender, age, etc.), clinical manifestation, laboratory test results, and imaging findings were electronically stored in a database managed by a professional team. Whole-body magnetic resonance angiography (MRA) was used instead of digital subtraction angiography (DSA) for the diagnosis and vascular evaluation of TAK. The MRA parameters were referred to our previous reports [15]. Echocardiography was administrated in the Philips iE33 system (Philips Medical Systems, Bothell, WA, USA), and assessed by two independent echocardiographic experts.

### Follow-up

The endpoint of observation was December 31, 2019. For naive or active patients, the visit was recommended once a month during the induction period and once per 3-month during the stable period. At each visit, the symptoms and signs were collected, and peripheral blood was extracted to determine the routine full blood count, erythrocyte sedimentation rate (ESR), hypersensitive C-reactive protein (hsCRP) and inflammatory factors such as interleukin-6 (IL-6) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). Echocardiography was performed during follow-up based on the condition of the TAK patients, or at an interval of 6 months.

## **Treatment**

TAK treatment includes the induction and stable period. Glucocorticoid is the first-line drug for TAK. The initial dose of prednisone or its equivalents was oral 40-60 mg per day and tapered to 10-15mg in about 6 months. A combination of immunosuppressants (such as cyclophosphamide [CTX], leflunomide [LEF] and mycophenolate mofetil [MMF], etc.) or biological preparations (TNF- $\alpha$  antibody [etanercept, adalimumab], IL-6 antibody [tocilizumab]) is essential to achieve remission and prevent relapse. The major treatment in the induction period included intravenous CTX 0.4-0.5g/m<sup>2</sup> per month, oral LEF 10-20mg per day and mycophenolate mofetil (MMF) 1.0-1.5g per day. After patients achieved clinical remission, intravenous CTX was always replaced by oral CTX or LEF in the stable period, while those oral induction drugs kept up but reduce their doses according to the condition of disease. To improve the symptoms of ischemia and maintain organ function, some patients will undergo surgical intervention. The cardiac surgery procedures include aortic valve replacement, mitral valvuloplasty, pulmonary artery stent implantation, coronary artery bypass surgery, and percutaneous transluminal angioplasty.

## **Subgrouping based on the severity of cardiac involvement**

Patients in severe group were those with severe valvular or atrioventricular lesions, heart function classified as NYHA III or IV, or both, and severe pulmonary hypertension with right heart structural changes and NYHA III or IV. Patients in mild-moderate group were those with mild to moderate valvular lesions, cardiac structural changes, and pulmonary hypertension with NYHA I or II. The other patients were considered as normal.

## **Definition of outcomes of cardiac structure and function**

The deterioration of cardiac structure was considered as new lesions or significant progression of structural parameters occurred, and the deterioration of cardiac function was defined as one grade of NYHA increased as described previously [16, 17]. The improvement of cardiac structure was defined as a decreased cardiac chamber, thinned septum or reduced valvular regurgitation on the echocardiography. Patients with clinical remission and reduced NYHA grade were defined as improvement in cardiac function. The others were considered stable or in maintenance.

## **Statistical analysis**

Continuous variables were described as median (Q1, Q3), while categorical variables were summarized as percentages. The Kruskal-Wallis test or Chi-square test was performed to compare the differences of baseline features among different subgroups. Variables that with  $P < 0.15$  in univariate analysis were chosen to perform Cox proportional-hazards regression multivariate models. Further, the risk factors that entered into the Cox regression models were also included in the matrix-based logistic regression to assess the probability of deterioration of cardiac structure and function. Kaplan Meier curve with log-rank test was applied to compare differences of free probability in the adverse outcomes of cardiac structure

and function between subgroups. Statistical significance was set at  $p < 0.05$  (two-sides). Analysis was performed using SPSS software (version 25.0; IBM Corp, Armonk, NY, USA).

## Results

### Baseline clinical characteristics of TAK patients

A total of 198 TAK patients who underwent echocardiography were enrolled in our study (Table 1). The male/female ratio was 1:3.6 (43 men, 155 women), and the median age of onset was 28.9 (21.8–42.0) years. The median disease duration at first echocardiography was 16.9 (2.8–55.1) months. With regard to TAK classification, Numano type V (46.0%, 91/198) was the most common type, followed by type I (23.7%, 47/198), type IIb (12.6%, 25/198). Moreover, 84.8% (168/198) of the patients were in active disease period. The common symptoms of cardiac dysfunction included chest distress (31.3%, 62/198), anhelation (25.8%, 51/198), and tachycardia (22.7%, 45/198). With regard to the NYHA classification, cases were categorized as NYHA I (52%, 103/198), NYHA II (25.8%, 51/198), NYHA III (16.6%, 33/198), and NYHA IV (5.6%, 11/198). There were 90 TAK patients (45.5%, 90/198) with hypertension, and 12 TAK patients (6.1%, 12/198) with coronary heart disease.

### Baseline echocardiographic characteristics of TAK patients

The general echocardiographic index is shown in Table 2. Cardiac structure abnormalities including valvular and atrioventricular abnormalities were observed in 60.1% (119/198) patients (Figure 2). There were totally 18.7% (37/198) of TAK patients with aortic foot dilatation, 14.1% (28/198) with ascending aorta widening, 8.1% (16/198) with pulmonary artery widening and 12.6% (25/198) with pulmonary artery hypertension. Patients were divided into 3 subgroups based on the severity of cardiac structure and function impairment, normal ( $n=55$ , 27.8%), mild-moderate ( $n=97$ , 49.0%) and severe ( $n=46$ , 23.2%) subgroups. There were statistical differences in cardiovascular parameters, atrioventricular parameters and ejection fraction among 3 subgroups ( $p < 0.001$ ).

Eighty-four patients (70.6%, 84/119) were found to have pathologically valvular abnormalities, including 58 cases (69.0%, 58/84) with single valve involvement and 26 cases (31.0%, 26/84) with more than one valve involvement. Aortic valves lesions (78.6%, 66/84) was the most commonly pathophysiological impairment. And there were 39.3% (33/84) and 21.4% (18/84) with mitral and tricuspid valves lesions respectively.

Furthermore, ninety-five patients (79.8%, 95/119) demonstrated atrioventricular abnormalities on echocardiography. Of patients with left ventricular enlargement, 72.7% (24/33) exhibited aortic involvement, and the rest exhibited mitral involvement and hypertension. With regard to left atrial dilatation, 42.9% (12/28) of patients had pulmonary hypertension and 53.6% (15/28) showed mitral valve involvement. All the patients with an enlarged right atrium had pulmonary hypertension and tricuspid valve involvement. Atrioventricular abnormalities combined with valvular lesions were noted in 60

patients, whereas pericardial effusion was only noted in 10 patients. In fact, 48 patients with cardiac structure lesions had a normal NYHA grade.

### **Comparison of the severity of cardiac structure and function impairment among subgroups**

The clinical characteristics of 3 subgroups are shown in Table 1. At baseline, the onset age ( $p<0.001$ ), NYHA grade ( $p<0.001$ ) and the rate of hypertension ( $p=0.035$ ) were significantly different among 3 subgroups. The frequency of cardiac dysfunction symptoms in the severe subgroup was markedly greater than those in the other two subgroups (all  $p<0.05$ ). There were no significant differences in gender, TAK classification or NIH score ( $p>0.05$ ). With respect to the laboratory test, the acute reactants like ESR, hsCRP, and proinflammatory cytokines such as TNF- $\alpha$  and IL-6 levels were elevated in TAK patients, although the differences across three subgroups were not significant (all  $p>0.05$ ).

### **Takayasu's arteritis-related treatment**

The medical treatments administered to TAK patients are described in Table 3. During the induced remission period, the median initial prednisone dose was 40 mg/day without difference between subgroups. There was no significant difference in the doses of anti-rheumatic drugs among 3 subgroups ( $p>0.05$ ) except leflunomide ( $p=0.041$ ). In terms of heart disease treatment, the largest number of angiotensin converting enzyme inhibitors (ACEI),  $\beta$ -receptor blockers, and digoxin, diuretic, and antilipemic drugs were used in the severe subgroup ( $p<0.05$ ).

Ten cases (7 cases in severe and 3 cases in mild-moderate group) underwent cardiac surgery and intervention, including aortic valve replacement, Bentall procedure, mitral valvuloplasty, pulmonary or coronary stent implantation and coronary artery bypass grafting.

### **Follow-up of cardiac structure and function**

A total 68.7% (136/198) of patients were followed up, and the remaining patients (31.3%, 62/198) did not review again because of continued treatment at the local hospital. The median follow-up duration was 28.6 (12.3-43.4) months. After rigorous analysis in cardiac structure, 42.7% (58/136) of patients had progression, 16.9% (23/136) had improved cardiac structure, and 40.4% (55/136) did not show any change. The total rate of cardiac functional progression, improvement, and maintenance was 22.8% (31/136), 12.5% (17/136), and 64.7% (88/136), respectively. The results of follow up for each subgroup are shown in Figure 3. The severe subgroup had the highest possibility of structural and functional deterioration ( $P<0.001$ ). Notably, 12.1% (24/198) of TAK patients at baseline had normal cardiac structure but impaired cardiac function due to angina pectoris and arrhythmia, and 25% (6/24) of these patients had worsened cardiac structure, including one with cardiac function deterioration during follow-up. Of 10 patients who underwent interventional surgery, 50% (5/10) had cardiac structure and function deterioration within half to eight years after surgery based on medical treatment.

Additionally, divided into two groups according to whether cardiac structure deteriorated, there was no significant difference in the doses of anti-rheumatic drugs among two groups. But more doses of ARB,  $\beta$ -

receptor blockers, and diuretic drugs were used in the worse group ( $p < 0.05$ ). There were 9 patients treated with TNF- $\alpha$  antibody, 20% (1/5) of the 5 patients who were followed up had cardiac structure and function deterioration, and another 20% had improved cardiac structure and function. Of the 12 patients treated with Tocilizumab, 2 cases (16.7%) had cardiac structure and function deterioration, one case (8.3%) had improved cardiac structure and function.

### **Risk factors for the deterioration of cardiac structure and function**

Cox regression showed that serum TNF- $\alpha$  level (HR=1.028, 95% CI 1.004-1.052,  $p = 0.021$ ), aortic regurgitation (HR=3.109, 95% CI 1.834-5.269,  $p < 0.001$ ) and ventricular hypertrophy (HR=2.090, 95% CI 1.242-3.518,  $p = 0.006$ ) at baseline were risk factors for the deterioration of cardiac structure. In addition, aortic regurgitation (HR=2.524, 95% CI 1.246-5.116,  $p = 0.010$ ) and ventricular hypertrophy (HR=2.500, 95% CI 1.224-5.108,  $p = 0.012$ ) at baseline correlated with worsening cardiac function significantly. Further, we constructed a matrix to stratify the patients confronting different risk of cardiac structure and function deterioration. The cases with higher serum TNF- $\alpha$  levels ( $\geq 8.1$  pg/ml), mild aortic regurgitation and ventricular hypertrophy at baseline had highest risk of structural progression at 83.4% (Figure 4A). Deterioration rate in mild aortic regurgitation group was significantly higher than the other two groups which already developed to moderate or severe regurgitation ( $P = 0.02$ ). Besides, patients with higher serum TNF- $\alpha$  levels ( $\geq 8.1$  pg/ml), moderate aortic regurgitation and ventricular hypertrophy at baseline might have a higher risk (66.2%) of worsening cardiac function (Figure 4B).

Using the normal subgroup as a control, the survival curve (Figure 5A and B) showed that the risk of worsening cardiac structure ( $p < 0.001$ ) and function ( $p < 0.001$ ) was greatest in the severe subgroup, with hazard ratios (HRs) of 16.2 (95% CI, 6.0-44.1) and 9.0 (95% CI, 3.3-24.5), respectively. The risk of worsening cardiac structure ( $p = 0.001$ ) in the mild-moderate subgroup was higher than the normal subgroup, with hazard ratios (HRs) of 4.8 (95% CI, 1.9–12.5), and there was no significant difference in the follow-up of cardiac function between those two subgroups ( $p > 0.05$ ). These findings suggest that the deterioration of cardiac structure and function was most apparent in the severe subgroup, despite treatments, and most cases experienced deterioration within the first 2 years from diagnosis.

### **Complications and death**

TAK patients often presented complications such as infection (50%, 68/136), particularly respiratory infection (75%, 51/68), and 47.1% (24/51) of these patients used preventive anti-tuberculosis drugs during treatment. The dynamic changes in inflammation indicators were not associated with cardiac structure and function deterioration ( $p > 0.05$ ). During follow-up, 3 cases of death were recorded. One patient had severe aortic regurgitation and ventricular hypertrophy, and eventually died of coagulopathy, respiratory, and circulatory failure. The causes of death in the other 2 cases were aortic dissection and cerebrovascular accident.

## **Discussion**

In this report, we provide a comprehensive description of cardiac structure and function changes in TAK patients in which we highlight the significance of early monitoring these changes in TAK patients with heart involvement and better management during treatment. The major advantage of our research is that it is based on a relatively large sample, providing a prospective study to investigate long-term cardiac outcomes and clarify risk factors for adverse cardiac structure and function in TAK population.

While previous study indicated that 8.6%-39.9% of TAK patients suffered from cardiac insufficiency [5, 6], 60.1% of patients in our cohort presented cardiac structure lesions, from which it can be concluded that they are not rare for Chinese TAK patients. For patients with cardiac insufficiency, their echocardiography often manifests as valvular regurgitation and cardiac chamber enlargement, particularly on aortic valve and left ventricle. In our study, nearly half of TAK patients were found to have cardiac dysfunction, primarily aortic regurgitation and left ventricular enlargement. Cardiac structure abnormalities are caused by various factors. Inflammation in TAK often starts from the aortic root, which may explain the high proportion of aortic valve lesions. And aortic valve regurgitation causes left cardiac chamber enlargement or eventually heart failure [18]. In our study, the percentage of TAK patients exhibiting coronary involvement was approximately 6.1% compared with previous finding of 10–30% [19]. Coronary wall inflammation can lead to myocardial ischemia, which further accelerates early coronary atherosclerosis. Secondary myocardial ischemia caused by stenosis and occlusion of coronary arteries is also a significant cause for death of TAK [20].

It is very necessary to monitor cardiac structure and function changes in TAK patients with heart involvement as cardiac complications are known as major causes for low quality of life for these patients [12]. During our research, the patients were classified into 3 subgroups according to the severity of their cardiac structure and function impairment. A total of 136 patients (68.7%) were followed up, and 31.3% of patients review echocardiography again because of continued treatment at the local hospital. By investigating the long-term outcomes of those who underwent more than two echocardiographic examinations, we found that the deterioration of cardiac structure and function occurred in all subgroups, but the highest incidence was in the severe subgroup. Additionally, although some patients did not present any symptoms related to cardiovascular system, this does not mean that these symptoms will not appear in the future. There were 3 deaths in our study related to cardiac insufficiency, aortic dissection and cardio-cerebrovascular events, which indicated that cardiac involvements and progression were closely related to poor prognosis of TAK patients.

According to cox regression analysis, serum TNF- $\alpha$  level ( $\geq 8.1$  pg/ml), aortic regurgitation and ventricular hypertrophy at baseline were the risk factors boosting cardiac structure deterioration. TNF- $\alpha$  is an important pro-inflammatory factor and plays an important role in tissue fibrosis [21]. TNF- $\alpha$  induces macrophages to produce IL-12, which can promote the differentiation of CD4 + T lymphocytes to Th1 cells and activate NK cells [22]. It has been confirmed by previous studies to be a key factor in the pathogenesis of TAK [23]. In this sense, elevated levels of TNF- $\alpha$  would suggest high levels of inflammation and subsequent fibrosis. Furthermore, several studies revealed that TNF- $\alpha$  directly promoted pressure overload-induced left ventricular hypertrophy and hypoxia-stimulated cardiac fibrosis,

which were major reasons for the deterioration of cardiac structure in TAK [24]. Apart from this, if patients have aortic regurgitation and ventricular hypertrophy in the early stage, their cardiac structure would be more likely to worsen. Interestingly, the deterioration rate in mild aortic regurgitation group was significantly higher than the other two which already developed to the stage of moderate to severe regurgitation ( $P = 0.02$ ). Finally, age and longer duration is also a critical risk factor for cardiovascular disease [25].

Although the prescription rates of glucocorticoids and immunosuppressive agents were quite close among the 3 subgroups during the period of induction and stabilization, the usage of drugs on improving cardiac function was higher for the severe subgroup, particularly digoxin and diuretic drugs, which was similar to the treatment during follow-up. When it comes to the TNF- $\alpha$  antibody, only 1 of 5 patients who have taken this drug suffered from cardiac structural deterioration. Since it is not widely used in clinical practice, no significant difference has been observed, so for further studies, more TNF- $\alpha$  antibody use for a larger sample size is needed. In the study, some severe patients exhibited improvements in disease through surgery. Analysis of the survival function curve indicates that it is quite essential to have active intervention during the first 2 years, a time when the cardiac function of patients is considerably impaired, so as to achieve better therapeutic effects and prolonged survival. Furthermore, the respiratory tract infection was quite frequent in the study, and TAK patients' immunity is rather low because of immunosuppressive agents, so it is indispensable to timely prevent or treat this kind of comorbidity.

There may be some limitations in this study. First, auxiliary inspection tests (electrocardiogram, cardiac magnetic resonance, etc.) would need to be performed in order to evaluate cardiac function more precisely in the future study. Second, missing values in the present study may affect the results to some extent. Further research is needed to confirm the conclusion.

## Conclusion

Heart involvement with TAK patients in echocardiography mainly manifests as pathologically valvular and atrioventricular abnormalities. To find out if there is heart involvement and progress, it's indispensable to regularly monitor the serum TNF- $\alpha$  level and cardiac structure especially aortic regurgitation and ventricular hypertrophy in TAK patients during the long-term follow-up.

## Abbreviations

Cyclophosphamide (CTX); digital subtraction angiography (DSA); erythrocyte sedimentation rate (ESR); hypersensitive C-reactive protein (hsCRP); interleukin-6 (IL-6); leflunomide (LEF); magnetic resonance angiography (MRA); mycophenolate mofetil (MMF); New York Heart Association (NYHA); Takayasu's arteritis (TAK); tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ).

## Declarations

## Acknowledgements

Not applicable.

## Funding

This work was supported by the National Science Foundation of China (No.81601398; No.81771730; No.81801598; No.81901639).

## Availability of data and materials

Please contact author for data requests.

## Authors' contributions

YJW and LLM contributed to acquire, analyze and interpret the clinical data and drafted the manuscript. LDJ conceived of the study and revised the manuscript critically. YY and YS performed the statistical analysis. YSW participated in the echocardiography examination. XMD, ZFJ, LYM and HYC participated in the design and coordination of the study. All authors read and approved the final version to be published.

## Ethics approval and consent to participate

This study has been approved by the Ethics Committee of Zhongshan Hospital, Fudan University [B2013-115(3)].

## Consent for publication

Informed written consent was obtained from each patient.

## Competing interests

The authors declare that they have no competing interests.

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## Tables

Table 1. Characteristics of Takayasu's arteritis patients.

Characteristic	Total	Normal	Mild-moderate	Severe	P value
<b>N</b>	198	55	97	46	
<b>Demographics</b>					
Sex					0.455
Female (%)	155(78.3)	40(72.7)	77(79.4)	38(82.6)	
Male (%)	43(21.7)	15(27.3)	20(20.6)	8(17.4)	
Onset age, years	28.9(21.8-42.0)	24.9(19.7-30.3)	29.6(21.5-41.7)	40.5(24.4-50.6)	<0.001
Duration, months	16.9(2.8-55.1)	10.1(2.2-39.6)	17.1(2.1-60.0)	24.1(9.0-94.7)	0.067
<b>Clinical manifestations</b>					
Hypertension (%)	90(45.5)	19(34.5)	53(54.6)	18(39.1)	0.035
Chest distress (%)	62(31.3)	1(1.8)	20(20.6)	41(89.1)	<0.001
Pectoralgia (%)	19(9.6)	2(3.6)	8(8.2)	9(19.6)	0.021
Tachycardia (%)	45(22.7)	1(1.8)	19(19.6)	25(54.3)	<0.001
Anhelation (%)	51(25.8)	-	12(12.4)	39(84.8)	<0.001
Dyspnea (%)	10(5.1)	-	-	10(21.7)	<0.001
<b>NYHA</b>					<0.001
I (%)	103(52.0)	55(100.0)	48(49.5)	-	
II (%)	51(25.8)	-	47(48.4)	4(8.7)	
III (%)	33(16.6)	-	2(2.1)	31(67.4)	
IV (%)	11(5.6)	-	-	11(23.9)	

<b>Laboratory findings</b>					
ESR, mm/h	29.0(13.0-60.0)	40.0(14.0-70.0)	24(12.5-58)	30.0(13.8-60.8)	0.339
hsCRP, mg/mL	9.1(1.8-33.0)	13.4(1.6-51.7)	8.4(1.8-25.1)	7.0(2.6-29.6)	0.607
TNF- $\alpha$ , pg/mL	8.0(5.9-10.4)	8.0(6.1-9.6)	7.3(5.8-10.2)	9.0(6.3-12.0)	0.192
IL-6, pg/mL	5.2(2.5-12.2)	5.6(2.8-13.0)	5.1(2.1-11.6)	5.2(3.2-12.9)	0.545
<b>NIH score</b>					<b>0.495</b>
0 (%)	8(4.1)	2(3.6)	6(6.2)	-	
1 (%)	22(11.1)	7(12.7)	9(9.3)	6(13.0)	
2 (%)	88(44.4)	19(34.5)	47(48.5)	22(47.8)	
3 (%)	66(33.3)	22(40.0)	28(28.9)	16(34.8)	
4 (%)	14(7.1)	5(9.1)	7(7.2)	2(4.3)	
<b>Numano angiographic classification</b>					<b>0.859</b>
Type I (%)	47(23.7)	15(27.3)	22(22.7)	10(21.7)	
Type IIa (%)	2(1.0)	-	1(1.0)	1(2.2)	
Type IIb (%)	25(12.6)	6(10.9)	15(15.5)	4(8.7)	
Type III (%)	13(6.6)	5(9.1)	5(5.2)	3(6.5)	
Type IV (%)	20(10.1)	6(10.9)	11(11.3)	3(6.5)	
Type V (%)	91(46.0)	23(41.8)	43(44.3)	25(54.3)	

ESR, erythrocyte sedimentation rate; hsCRP, hypersensitive C-reactive protein; IL-6, interleukin-6; and TNF- $\alpha$ , tumor necrosis factor- $\alpha$ .

Table 2. Echocardiographic values in patients with Takayasu's arteritis in different groups.

	Total	Normal	Mild-moderate	Severe	P value
<b>Cardiovascular parameters</b>					
Aortic foot diameter, mm	31(28-34)	29(27-32)	31(29-34)	32.5(30-36)	<0.001
Pulmonary artery pressure, mmHg	32(28-35)	30(26.5-33)	31(28-35)	39(32-53)	<0.001
<b>Atrioventricular parameters</b>					
LA diameter, mm	34.5(31.8-39)	32(30-34)	35(32-39)	40(35-42.8)	<0.001
LV end-systolic diameter, mm	29(27-33)	27(26-29)	30(28-32)	35.5(28.3-45)	<0.001
LV end-diastolic diameter, mm	46.5(43-51.3)	44(41.8-46.3)	47(43.3-50)	54(44.3-60)	<0.001
Septal thickness, mm	9(8-11)	8(8-9)	10(9-11)	11(9-12)	<0.001
<b>Ejection fraction, %</b>	66(61-69)	68(66-69.3)	65(62-68)	60(48-66.5)	<0.001

LA, left atrial; and LV, left ventricle.

Table 3. Medical treatment of 198 patients with Takayasu's arteritis.

Drugs	Normal	Mild-moderate	Severe	P value
Prednisone, mg	40(32.5-50)	40(20-50)	40(30-50)	0.121
Cyclophosphamide (%)	19(34.5)	31(32.0)	13(28.3)	0.795
Leflunomide (%)	30(54.5)	38(39.2)	14(30.4)	0.041
Mycophenolate mofetil (%)	16(29.1)	14(14.4)	7(15.2)	0.066
Hydroxychloroquine (%)	31(56.4)	43(44.3)	22(47.8)	0.360
Adalimumab (%)	-	-	2(4.3)	0.036
Etanercept (%)	4(7.3)	3(3.1)	-	0.136
Tocilizumab (%)	6(10.9)	5(5.2)	1(2.2)	0.163
CCB (%)	22(40)	52(53.6)	17(37.0)	0.102
ACEI (%)	7(12.7)	7(7.2)	12(26.1)	0.008
ARB (%)	5(9.1)	15(15.5)	7(15.2)	0.512
$\beta$ -receptor blockers (%)	16(29.1)	45(46.4)	29(63.0)	0.003
Digoxin (%)	-	1(1.0)	10(21.7)	<0.001
Diuretic (%)	7(12.7)	19(19.6)	28(60.9)	<0.001
Anticoagulant drug (%)	31(56.4)	58(59.8)	34(73.9)	0.156
Antilipemic agent (%)	10(18.2)	26(26.8)	23(50.0)	0.002

CCB, calcium channel blockers; ACEI, angiotensin converting enzyme inhibitors; and ARB, angiotensin receptor blockers.

## Figures

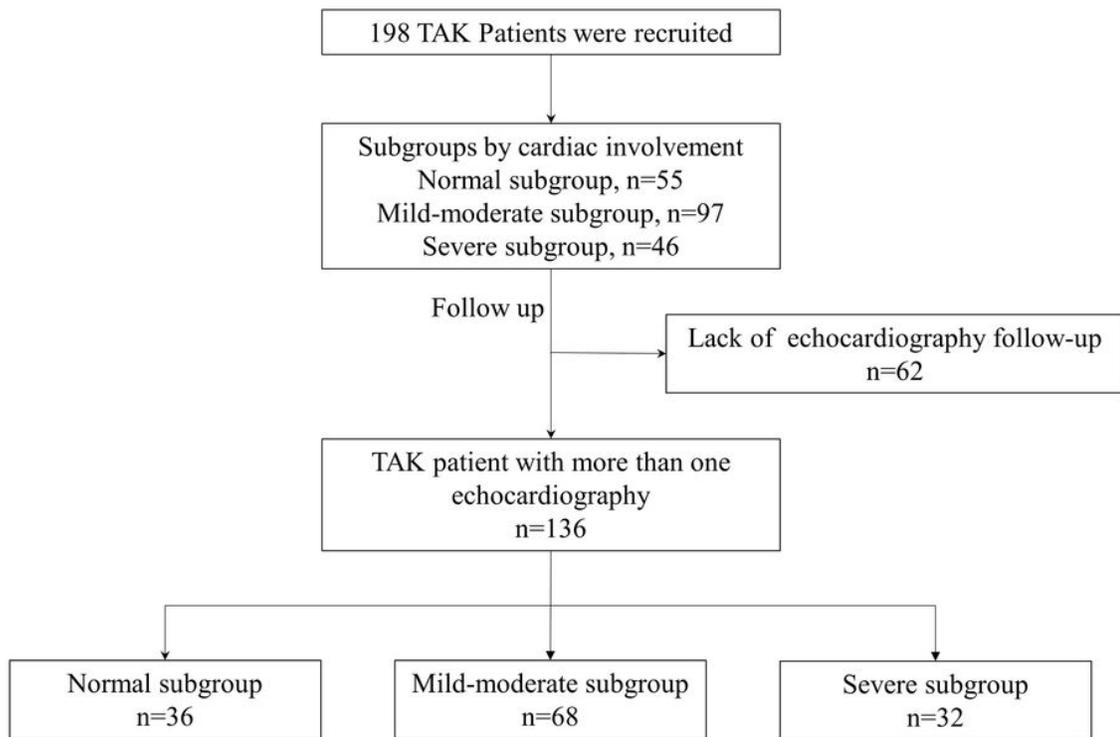
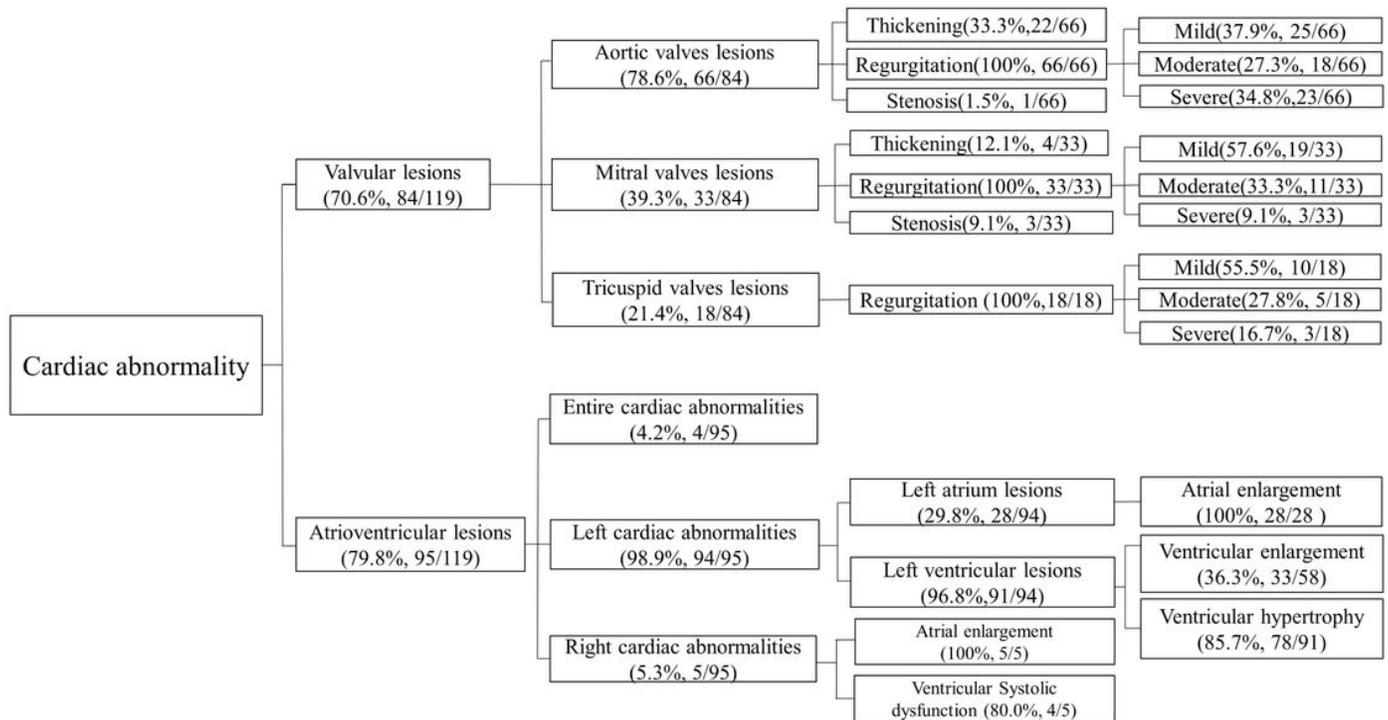


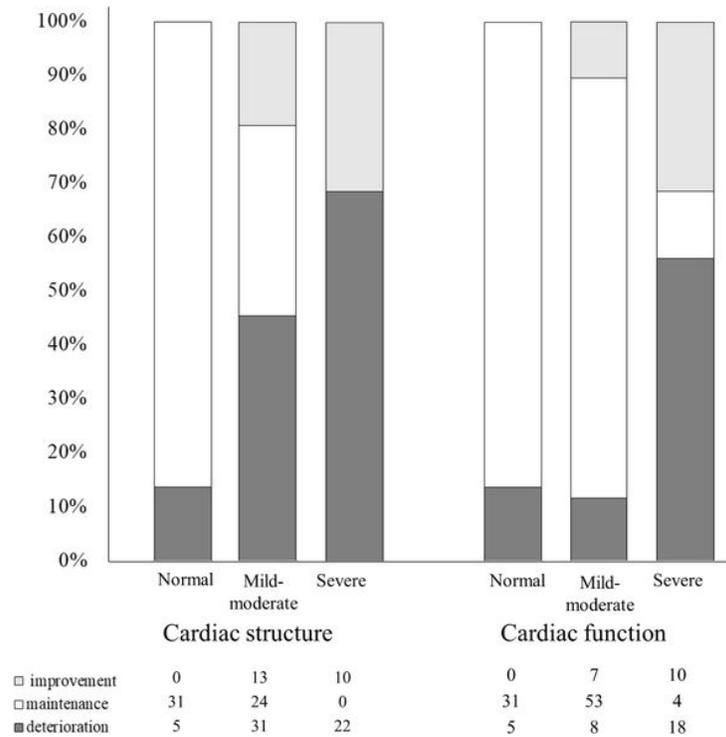
Figure 1

Study design.



**Figure 2**

Abnormal findings of echocardiography in TAK patients. Cardiac abnormality is classified into valvular and atrioventricular abnormalities. The detailed classification, proportion and number of patients are shown in the figure.



**Figure 3**

Distribution of long-term outcomes in three subgroups of severity. Three outcomes of cardiac structure and function are identified: deterioration (black), maintenance (white) and improvement (gray). The severe subgroup has the highest rate of structural and functional deterioration( $p < 0.001$ ). Detailed values of each subgroup are shown in the figure.

**A**

No aortic regurgitation	17.0%	37.1%	No ventricular hypertrophy
	24.9%	48.9%	Ventricular hypertrophy
Mild aortic regurgitation	51.7%	75.5%	No ventricular hypertrophy
	63.5%	83.4%	Ventricular hypertrophy
Moderate aortic regurgitation	34.3%	60.1%	No ventricular hypertrophy
	45.9%	71.0%	Ventricular hypertrophy
Severe aortic regurgitation	23.8%	47.4%	No ventricular hypertrophy
	33.7%	59.4%	Ventricular hypertrophy
	TNF- $\alpha$ normal	TNF- $\alpha$ abnormal	

■ < 40%  
■ 40 -60%  
■ > 60%

**B**

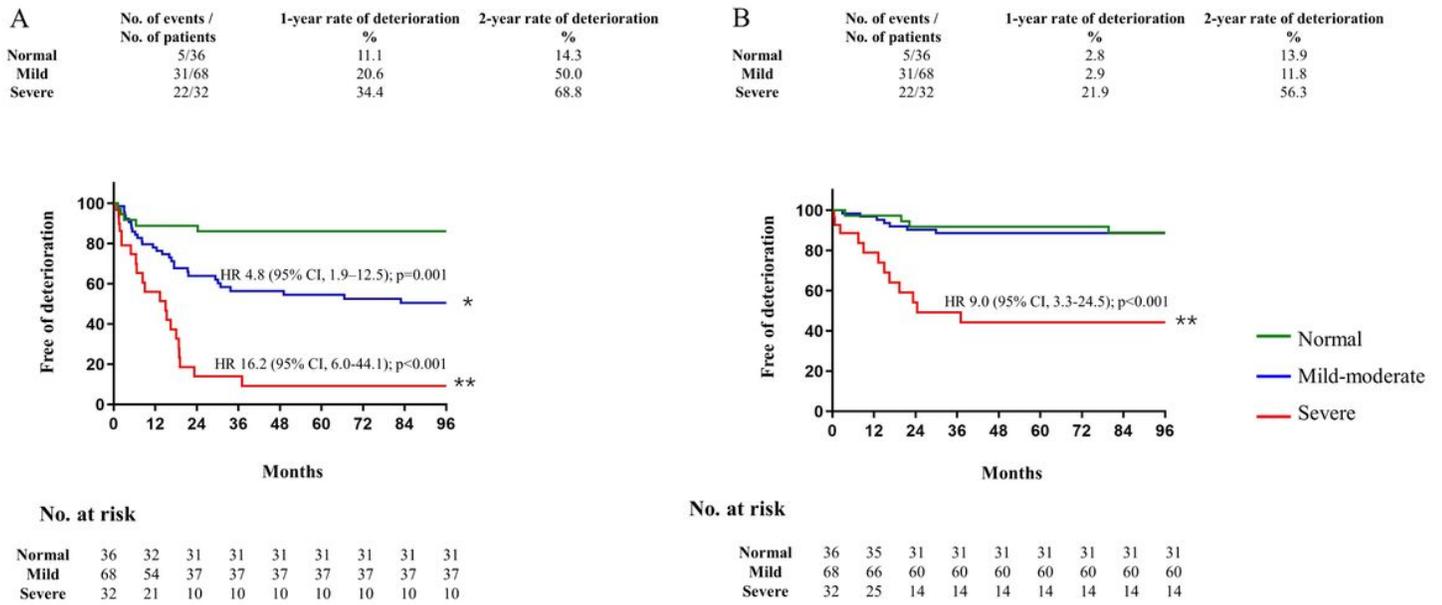
No aortic regurgitation	5.8%	17.1%	No ventricular hypertrophy
	13.3%	33.9%	Ventricular hypertrophy
Mild aortic regurgitation	11.3%	29.7%	No ventricular hypertrophy
	24.0%	51.2%	Ventricular hypertrophy
Moderate aortic regurgitation	19.1%	44.1%	No ventricular hypertrophy
	37.1%	66.2%	Ventricular hypertrophy
Severe aortic regurgitation	9.1%	25.0%	No ventricular hypertrophy
	19.9%	45.3%	Ventricular hypertrophy
	TNF- $\alpha$ normal	TNF- $\alpha$ abnormal	

■ < 20%  
■ 20 -40%  
■ > 40%

**Figure 4**

Matrix-based logistic regression models: A: Matrix model for predicting risk of cardiac structure deterioration. Based on serum TNF- $\alpha$  level ( $\geq 8.1$  pg/ml), aortic regurgitation, ventricular hypertrophy and hypertension at baseline, patients could be separated into three risk groups: high risk (red,  $\geq 60\%$ ), moderate (yellow, between 40 and 60%) and low risk (green,  $\leq 40\%$ ). B: Matrix model for predicting risk of cardiac function deterioration. Based on serum TNF- $\alpha$  level ( $\geq 8.1$  pg/ml), aortic regurgitation and ventricular hypertrophy at baseline, patients could be separated into three risk groups: high risk (red,  $\geq 40\%$ ), moderate (yellow, between 20 and 40%) and low risk (green,  $\leq 20\%$ ).

Survival curve indicating the deterioration rate of cardiac structure and function in three groups.



**Figure 5**

Survival curves of free possibility of adverse outcomes in different subgroups. A: For cardiac structure. The risk of worsening cardiac structure was greatest in the severe subgroup. Comparison with normal subgroup, the hazard ratio of severe subgroup (\*\*) for cardiac structure deterioration is 16.2(p<0.001). Comparison with mild-moderate subgroup (\*), the hazard ratio of severe subgroup is 4.8(p<0.001). B: For cardiac function. The risk of worsening cardiac function is greatest in the severe subgroup. Comparison with normal subgroup (\*\*), the hazard ratio of severe subgroup for cardiac function deterioration is 9.0 (p=0.001). There was no significant difference in the follow-up of cardiac function between normal and mild-moderate subgroup (p> 0.05).